Nicotine differentially modulates antisaccade performance in healthy male non-smoking volunteers stratified for low and high accuracy

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Abstract: RATIONALE: Nicotinergic agents are currently examined as possible pro-cognitive drugs for a variety of clinical conditions marked by cognitive deficits, such as attention deficit hyperactivity disorder (ADHD) or schizophrenia. The response to acute nicotine is heterogeneous across subjects and samples; however, only a few reliable predictors of response have been identified. OBJECTIVES: We tested the hypothesis that baseline performance level in cognitive control may be a predictor of the cognitive effects of nicotine. METHODS: We tested 28 healthy Caucasian, male, non-smoking volunteers with the antisaccade task, an oculomotor measure of cognitive control. Participants were given a 7-mg nicotine patch in a double-blind, placebo-controlled, counterbalanced, within-subjects design. Subjects were stratified into high and low performers based on their antisaccade error rate in the placebo condition (median split). RESULTS: Nicotine tended to reduce response time variability of prosaccade latency ($p = 0.06$). There was no main effect of nicotine on antisaccade error rate ($p = 0.31$). However, nicotine significantly reduced antisaccade error rate in the low-accuracy probands while leaving performance of the high-accuracy probands unaffected (interaction, $p < 0.05$). Furthermore, we found a nicotine-induced reduction of response time variability of antisaccade latency at one target location in the low-performing group (interaction, $p < 0.05$). CONCLUSIONS: The present results demonstrate the importance of baseline performance differences for the effectiveness of pharmacological enhancement of cognitive control. More generally, the results suggest that stimulation of the nicotinic acetylcholine receptor system might be an effective way of improving cognition in people with poor cognitive performance, such as patients with ADHD or schizophrenia.

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Nicotine differentially modulates antisaccade performance in healthy male non-smoking volunteers stratified for low and high accuracy

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Abstract

Rationale: Nicotinergic agents are currently being examined as possible pro-cognitive drugs for a variety of clinical conditions marked by cognitive deficits, such as attention deficit hyperactivity disorder (ADHD) or schizophrenia. The response to acute nicotine is heterogeneous across subjects and samples; however, only few reliable predictors of response have been identified. *Objectives:* We tested the hypothesis that baseline performance level in cognitive control may be a predictor of the cognitive effects of nicotine. *Methods:* We tested 28 healthy Caucasian, male, non-smoking volunteers with the antisaccade task, an oculomotor measure of cognitive control. Participants were given a 7-mg nicotine patch in a double-blind, placebo-controlled, counterbalanced, within-subjects design. Subjects were stratified into high and low performers based on their antisaccade error rate in the placebo condition (median-split). *Results:* Nicotine tended to reduce response time variability of prosaccade latency ($p=0.06$). There was no main effect of nicotine on antisaccade error rate ($p=0.31$). However, nicotine significantly reduced antisaccade error rate in the low accuracy probands while leaving performance of the high accuracy probands unaffected (interaction $p<0.05$). Furthermore, we found a nicotine-induced reduction of response time variability of antisaccade latency at one target location in the low performing group (interaction $p<0.05$). *Conclusions:* The present results demonstrate the importance of baseline performance differences for the effectiveness of pharmacological enhancement of cognitive control. More generally, the results confirmed that stimulation of the nicotinic acetylcholine receptor (nAchR) system might be an effective way of improving cognition in people with poor cognitive performance, such as patients with ADHD or schizophrenia.

Keywords

Nicotine, acetylcholine, executive function, antisaccade, oculomotor control, attention

Introduction

In the last decades growing interest in the pro-cognitive effects of nicotine has emerged. Earlier research mostly studied effects of nicotine or smoking in deprived smokers (Heishman et al. 1994). A limitation of studying nicotine effects in smokers is that putative genuine cognitive enhancing effects of the compound cannot be disentangled from the reversal of withdrawal-induced performance deficits (Heishman et al. 1994). More recent studies have taken this methodological problem into account by testing effects of nicotine in non-deprived smokers, minimally deprived smokers (deprivation for less than 2 hours), or non-smokers (Heishman et al. 2010). A recent meta-analysis by Heishman et al. (2010) found significant positive effects of nicotine on six cognitive domains: fine motor, alerting attention-accuracy and response time (RT), orienting attention-RT, short-term episodic memory-accuracy, and working memory-RT. Some performance domains could not be included in the meta-analysis as there were not sufficient numbers of studies available in these domains such as reasoning, arithmetic and executive function (Heishman et al. 2010).

Therefore, more studies of nicotine effects on executive functioning are needed, especially as there is an unmet need for satisfactory treatment of attention and executive control deficits in psychiatric disorders. Particularly in schizophrenia, cognitive symptoms such as deficits in executive control have the most substantial impact on illness outcome (Friedman et al. 1999). Executive deficits prevent the schizophrenia patient from retaining or relearning skills that are necessary in order for them to function within and be re-integrated into the community. Therefore, it is hypothesized that improvement of these executive deficits would lead to an improved outcome (Friedman et al. 1999). Thus, it is of particular relevance to find new ways of treating executive dysfunctions and a recent meta-analysis demonstrated that the adjunctive treatment with cholinergic substances might be useful for remediation (Ribeiz et al. 2010).

Another aspect in nicotine research that has mostly been disregarded concerns inter-individual differences in treatment response. These inter-individual differences might partially explain why some studies showed beneficial effects of nicotine but others did not. Parallel to earlier findings regarding the dopamine system, Newhouse et al. (2004) suggest an inverted-U shaped function of baseline differences in performance and nicotinic stimulation. Depending on the baseline level of cognitive performance, an equivalent degree of nicotinic stimulation can either enhance or impair performance. While in low-performing subjects nicotine improves performance and brings performance closer to the optimum, already high-performing subjects are impaired by nicotine intake (Newhouse et al. 2004).

Therefore, in studies of the effects of nicotinic agonists it would be important to systematically consider the role of baseline performance levels in order to explain inter-individual variability in drug response. So far, there are only a few psychopharmacological studies in performance-stratified samples, and only one published study which investigated nicotine. Three studies investigated differential psychopharmacological effects with measures of central inhibition or gating: prepulse inhibition (PPI) of the acoustic startle response and suppression of the P50 event-related potential in a condition-test paradigm (P50 gating) (Csomor et al. 2008; Knott et al. 2010; Vollenweider et al. 2006). Both gating processes provide the individual with the ability to negotiate a sensory-laden environment by blocking out excess or trivial stimuli so that an individual can focus attention on the most salient aspects of the stimulus-laden environment (Braff et al. 2001; Potter et al. 2006). Vollenweider et al. (2006) demonstrated that the antipsychotic clozapine significantly increased PPI levels in low PPI performers but showed no effect in high PPI performers. Likewise, Csomor et al. (2008) found that haloperidol failed to increase PPI in low PPI performers, but attenuated PPI in high PPI performers. Moreover, haloperidol increased P50 gating in low suppressors and disrupted P50 gating in high

suppressors (Csomor et al. 2008). A recent study by Knott et al. (2010) demonstrated that nicotine reduced P50 gating in high suppressors while P50 in low suppressors remained unaffected by nicotine. Allman et al. (2010) found that low antisaccade performers with long-latency antisaccades exhibited shorter antisaccade latencies on D-amphetamine while high performing subjects with short-latency antisaccades had longer latencies on D-amphetamine (Allman et al. 2010).

To our knowledge, there is no study on inter-individual effects of nicotine employing the antisaccade task. Therefore, the present study aimed to investigate the effects of nicotine on the antisaccade task in performance-stratified subgroups of healthy, non-smoking volunteers. In the antisaccade task, participants must suppress the reflexive urge to look at a visual target that appears suddenly in the peripheral visual field and must instead look away from the target in the opposite direction (Munoz and Everling 2004). The ability to control behavior flexibly, responding automatically to stimuli in one situation and suppressing this automatic response in favor of an alternative response in a different situation, is one of the key components of executive control. The saccadic eye movement system provides an excellent model for investigating this ability of the brain because eye movements are easy to measure in the laboratory with high test-retest reliability (Ettinger et al. 2003; Klein and Ettinger 2008; Munoz and Everling 2004,). Moreover, the antisaccade task recruits a well-defined fronto-parieto-subcortical network (Ettinger et al. 2008; Munoz and Everling, 2004) and is considered a schizophrenia endophenotype (Calkins et al. 2008). Furthermore, previous studies demonstrated the sensitivity of the antisaccade task to nicotine administration in schizophrenia patients (Dépatie et al. 2002; Larrison-Faucher et al. 2004) and in healthy subjects (Bowling and Donnelly, 2010; Dawkins et al. 2007; Dépatie et al. 2002; Ettinger et al. 2009; Rycroft et al. 2006; Rycroft et al. 2007). Based on the model by Newhouse et al. (2004), we hypothesized that participants showing low

performance on the antisaccade task would benefit from nicotine administration while already high-performing participants would be impaired by nicotinic stimulation.

Methods and materials

Subjects

Before conducting our study, we performed an a priori power analysis using G*Power 3.1.2 (Faul et al. 2007). We chose to perform the power calculation on antisaccade error rate as the dependent variable as this is the most frequently studied measure of this task. We chose a medium effect size of Cohen's f=0.15 (Cohen, 1988) and took the correlation of r=0.89 among repeated measures from empirical evidence of a test-retest reliability study (Ettinger et al. 2003). The required minimum sample size was N=22. Therefore, we aimed at measuring about 30 subjects to ensure a sufficiently large sample size.

Thirty healthy Caucasian, non-smoking, male volunteers were recruited from the local community by advertisement at the university and by contacting a random sample of the inhabitants of Bonn based on a list from the city registry. Non-smokers in our sample were defined as individuals who had smoked no more than 100 cigarettes during their lifetime and had not smoked in the past year. The volunteers were required to be between 18 and 55 years old and were screened for the exclusion criteria and interviewed with the Structured Clinical Interview for DSM-IV (SCID, German version: Wittchen, Wunderlich, Gruschwitz & Zaudig, 1997). Exclusion criteria were a current or lifetime Axis I disorder, a first-degree relative with psychosis, a history of neurological illness or another severe medical condition, head injury with loss of consciousness of > 5 min, lifetime history of alcohol or substance abuse or dependence, visual impairments, obesity (body mass index BMI between 20 and 30), intake of any medications which act on the CNS. Furthermore, the following exclusion criteria regarding nicotine application were employed: cardiovascular disease, hypertension, atopic or eczematous dermatitis (due to localised patch sensitivity), severe renal or hepatic impairment or active peptic ulcers, hyperthyroidism, pheochromocytoma, insulin-dependent diabetes, hypersensitivity to

patches, hypersensitivity to nicotine, or any of the excipients of the patches. Subjects were allowed to drink their usual amount of coffee, tea or other caffeine-containing beverages in the morning. Caffeine consumption was documented for both testing sessions. Verbal IQ of all subjects was estimated with a standardised German vocabulary test, the MWT-B (Mehrfachwahl-Wortschatz-Intelligenztest, Lehrl, 1989). Approval of the local ethics committee and the German Federal Institute for Drugs and Medical Devices (BfArM) was obtained and the study was registered with http://www.clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT01315002). Participants provided written informed consent before inclusion.

Experimental design and nicotine application

Each subject underwent telephone-screening for a first check for the inclusion and exclusion criteria of the present study. Subsequently, subjects were invited to the laboratory for two testing sessions preferably with a time interval of one week between the two sessions. Before session one, blood pressure was taken to ensure no subject suffered from undetected hypertension (diastolic value no greater than 90, World Health Organization 2003). On both testing days, a urine drug screening test was applied before patch application to ensure subjects had abstained from amphetamine, benzodiazepine, cocaine, THC cannabinoides, and opiate/morphine (nal von minden, Moers, Germany).

Nicotine was applied in a double-blind, placebo-controlled, counterbalanced within-subjects design. Subjects received nicotine via a patch (NiQuitin Clear 7 mg, Glaxo Smith Cline, Germany) and were given a placebo patch (Fink and Walter GmbH, Germany) of similar appearance. Both patches were applied to the upper back of the subject by a research assistant who was not running the test sessions in order to ensure double-blindness. Testing with the antisaccade paradigm commenced 3 hours after patch application. Nicotine administration using

the NiQuitin patch generates a fast-rising nicotine plasma level (a nicotine plateau level is achieved after 2 to 4 hours after application according to the Summary of Product Characteristics of NiQuitin Clear). The 7 mg nicotine dosage was chosen as prior studies employed similar dosages and found cognitive effects in non-smokers in the absence of significant side effects (see Barr et al. 2008; Levin et al. 1998; Poltavski & Petros 2006). Therefore, only a low drop-out rate due to side-effects was expected. At the end of each testing session the patch was removed by the research assistant and participants were asked which patch they thought they had received. Mood ratings and physical symptom ratings were assessed with visual analogue scales. In each case there was an item beside a horizontal line of 100 mm in length, ranging from "strongly disagree" at the one end (0) to "strongly agree" at the other end (100). The participants had to indicate their perception of their current state by marking the point on the horizontal line they think is most appropriate. The following items were included: "relaxed", "alert", "nervous", "drowsy", "comfortable", "fidgety", "concentrated", "dizzy", "excited", "attentive", "I like the substance", "I am in a bad mood", "I feel nauseous", and "I am in a good mood". After completing the second session, participants were debriefed and compensated with € 80 (about $ 112) for their participation. A schematic overview of the timeline is depicted in Table 1.

Table 1 about here

Saccadic tasks

Participants were seated 41 cm from a 17-inch monitor, head movements were minimized using a chinrest. The testing room was quiet and dimly lit. Experimental stimuli were presented using ERTS® (BeriSoft Corporation, Frankfurt, Germany). Participants performed one block of prosaccade trials and one block of antisaccade trials. The order was fixed beginning with the

prosaccade trials. For both tasks, subjects fixated a white central fixation cross on a black background. The fixation cross appeared for 1000, 1500, 2000 or 2500 ms at random. A peripheral target (a white dot) then appeared at 6° or 12° either to the left or to the right of the central fixation cross for a duration of 1000 ms. The central fixation cross was extinguished whenever the peripheral target appeared (step paradigm). Altogether, there were 96 trials (48 prosaccade and 48 antisaccade trials), in each case consisting of 12 trials×4 target positions. The sequence of peripheral target presentations was pseudorandomised. There were five practice trials before each block which were not included in the analysis. The prosaccade instruction was to look toward the peripheral target as quickly and as accurately as possible (serving as an easy control task for the antisaccade task). In the antisaccade task, subjects were instructed not to look toward the target but to look away from the peripheral target to the mirror position on the opposite side of the computer screen as quickly and as accurately as possible.

Eye movement recording and analysis

Eye movements were recorded using electroocculogram (EOG). Five nonpolarizable Ag/AgCl electrodes (Easycap GmbH, Herrsching-Breitbrunn, Germany) were employed. Two electrodes recorded the horizontal electroocculogram (HEOG) from the outer canthi of the eyes, and another two electrodes recorded the vertical electroocculogram (VEOG) from supra- to suborbital sites of the right eye to detect eye blinks. A ground electrode was placed on the glabella. The electrolyte gel Abralyte® 2000 (Easycap GmbH, Herrsching-Breitbrunn, Germany) was used as an abrasive paste to minimise skin impedance level and as a conducting agent between skin and electrode. The impedance was kept below 5 kΩ at all electrode locations and checked at the beginning of each recording session. The EOG was recorded using Neuro Scan Labs™ with a Synamps® 5083 amplifier controlled by Acquire® software package (Neurosoft

Inc., Sterling USA). EOG data were digitized at 250 Hz and stored on hard disk for later analysis. Simultaneously with each presentation of the target dot, a trigger marker (indicating at which position the dot was shown) was recorded. Trigger markers were stored together with the EOG data for later segmentation and analysis of the eye movement data.

The analysis of the EOG data was performed with Brain Vision Analyzer and Matlab. At first, the raw data pre-processed with Brain Vision Analyzer. Sampling rate was set to 250 Hz and the raw data was segmented relative to the trigger marker positions. That is, a segment started 200 ms before the onset of a trigger marker and ended 800 ms after a trigger marker (segment length= 1000 ms). Next, the data was filtered with a high cut-off filter of 30,000 Hz and with a notch filter of 50 Hz and baseline correction was employed.

After initial processing, the data were analysed by a Brain Vision Analyzer macro program searching for the saccadic eye movements in the HEOG channel. The automatic detection of saccades used the criteria of minimum amplitude (1°) and velocity (30°/s). Whenever there was such a deviation from the baseline, the onset and offset of the saccade was marked with markers categorizing the saccade into directional correct prosaccade, prosaccade direction error, directional correct antisaccade, or antisaccade direction error. Subsequently, the data was visually inspected by one of two raters blind to experimental condition (placebo/nicotine). The rater verified whether saccades were correctly identified by the program and changed markers categorizing the saccade where applicable. In addition, the rater rejected segments (=trials) if the subject's latency to respond was below 80 ms (=anticipatory response), if the subject did not respond (amplitude less than 3°), or if the subject blinked immediately before the target appearance or during the saccade. For the low accuracy probands, 47.50±0.81 (98.96±1.68%) of prosaccade trials and 46.82±1.66 (97.54±3.46%) of antisaccade trials were valid trials. For the high accuracy probands, 47.71±0.47 (99.40±0.98%) of prosaccade trials and 47.64±0.46

(99.26±0.95%) of antisaccade trials were valid trials. Low and high accuracy probands did not differ regarding the number of valid trials both for prosaccade trials ($F(1,25)=0.90$, $p=.77$) and for antisaccade trials ($F(1,25)=1.14$, $p=.30$). In addition, there were no main or interaction effects regarding nicotine treatment on number of valid trials (all $p>.32$).

The dependent variables were saccade latencies (time between target appearance and saccade initiation of correct trials) and percentage saccade errors (an amplitude of the first saccade after target appearance greater than 3° in the wrong direction) and intra-individual coefficient of variation (ICV=standard deviation of saccade latency/mean saccade latency; ICV provides a measure of response variability, adjusted for the influence of response speed (Nandam et al., 2011)).. A prosaccade (direction) error was counted when the first saccade after target appearance was away from the target; an antisaccade (direction) error was detected when the first saccade after appearance of the peripheral target was performed towards the target. The error rate was calculated as the percentage of error trials over the total number of valid saccade trials (excluding e.g. eye-blink trials). In addition, the proportion of corrected antisaccade errors was collected to control whether the subjects understood the task and made an effort to correctly perform the task. A corrected antisaccade error was scored when a corrective saccade away from the target was made after the subject had made an antisaccade error.

Statistical analyses

Statistical analyses were conducted using the software PASW Statistics 18 (SPSS Inc., Chicago, IL USA). To test whether nicotine had a differential effect on subjects with high antisaccade error rates (i.e. low accuracy) versus subjects with low antisaccade error rates (i.e. high accuracy), subjects were divided by a median-split procedure into low and high accuracy probands. This median-split was based on the mean antisaccade error rate of both eccentricities

(6° and 12°) of the placebo session. For the statistical analysis of nicotine effects on saccadic variables 2×2×2×2 repeated-measures analyses of covariance (ANCOVA) with verbal IQ as a covariate were calculated with Treatment (placebo, nicotine) and Eccentricity (6° eccentricity, 12° eccentricity) as within-subjects factors and Group (low accuracy probands, high accuracy probands) and Order (nicotine first, placebo first) as between-subjects factors. Verbal IQ was entered as a covariate in all analyses as the high and low accuracy groups differed on this variable (see below). Assessment of the participants' blindness for patch treatment was evaluated with chi-squared tests. Data from the visual analogue scales assessing physical symptoms and mood ratings were analysed with 2×2×2 repeated-measures analyses of variance (ANOVA) with Treatment (placebo, nicotine) as within-subjects factor, and Time (first assessment, second assessment) and Group (low accuracy probands, high accuracy probands) as a between-subjects factors. The significance level of all statistical tests was set at $p<.05$.

Results

Sample characteristics

Two subjects dropped out of the study due to nausea, one of these subjects also experienced vomiting. Unblinding showed that in both cases the subjects had been administered nicotine. We replaced the two drop-outs by recruiting two additional subjects. Thus, data of thirty subjects were analyzed. Exploratory data analysis identified one subject as an outlier on the antisaccade error rate (more than three times of the interquartile range of the boxplot); this subject was excluded from further analyses. The final sample therefore included 29 subjects. The mean time interval between the two testing sessions was 9.28 days (SD=5.18). The median antisaccade error rate was 25.91 %. Removal of the median subject led to two groups of n=14 each. The mean age of these 28 subjects was 28.11 (SD=9.22) years, the median age was 25 years; age ranged from 20 to 55 years. Sample characteristics are summarized in Table 2. The two groups did not differ in age, years of education, or BMI. The two groups differed regarding verbal IQ, indicating lower verbal IQ in high accuracy probands. Therefore, verbal IQ was entered as a covariate in the subsequent analyses of variance. Thirteen of the 28 subjects received nicotine first and fifteen received placebo first. The frequencies of patch order in the low and high accuracy groups did not significantly differ from the expected patch order ($\chi^2(1)=1.29$; p=.26).

Table 2 about here

Blindness for patch treatment and mood/physical symptoms ratings

Participants were able to correctly identify the nicotine patch. For session 1, participants correctly guessed on the nicotine patch with a probability of 69.2 % which was significantly

above chance level ($\chi^2(1)=4.14$; p=.042). For session 2, participants correctly guessed they had nicotine with a probability of 92.3% ($\chi^2(1)=16.45$; p=.0001). These results reveal that despite employing a double-blind design, the participants could tell the difference between administration of nicotine and placebo, especially after session 2 when participants were able to compare both sessions. Correct guessing was not associated with group status: there was no difference in correct guessing rate in low and high accuracy probands (session 1: $\chi^2(1)=0.16$; p=.69; session 2: $\chi^2(1)=0.47$; p=.50).

Results from the visual analogue scales on mood and physical symptoms demonstrated that probands experienced side effects from the nicotine administration. Significant interaction effects of Time×Treatment indicated that, compared to the first assessment without a patch, for the second assessment (i.e. after three hours of nicotine patch application) probands felt more fidgety ($F(1,26)=6.46$ p=.017 $\eta_p^2=.20$), more nauseous ($F(1,26)=5.04$ p=.034 $\eta_p^2=.16$), and, by trend, the probands felt less comfortable ($F(1,26)=4.25$ p=.050 $\eta_p^2=.14$). Therefore, it is very likely that probands correctly identified the nicotine patch on the basis of side effects caused by the nicotine treatment.

Reliabilities of saccadic variables

Saccades were rated by two raters. To assess the consistence of performance in one rater (intrarater reliability), internal consistency was assessed using Cronbach's coefficient alpha. Interrater reliability of the two raters was assessed by computing intraclass correlations (ICC) with ICC (3,2) (two-way mixed average measures, absolute agreement). All reliability analyses were performed on 12 randomly chosen subjects. Raters were blind to group and treatment status. Both intrarater and interrater reliabilities were high (all coefficients > 0.97).

Saccadic performance: correction of antisaccade errors

The average correction rate of antisaccade errors was high (placebo condition: mean 95.64%, SD=7.62; nicotine condition: mean 90.82%, SD=17.51). For the low accuracy probands mean correction rate under placebo was 92.97% (SD=9.66), under nicotine it was 89.90% (SD=17.92). The high accuracy probands exhibited mean correction rates of 98.30% (SD=3.46) in the placebo condition and 91.74% (SD=17.72) in the nicotine condition. These high proportions of corrected antisaccade errors indicate that subjects understood the task and were willing to perform the task. Groups did not differ in antisaccade correction rates ($F(1,23)=0.80$, $p=.78$), and there were no further main or interaction effects for this variable (all $p>.35$).

Saccadic performance: effects of eccentricity and nicotine

Exploratory data analysis revealed that there was almost no variance in prosaccade error rate indicating subjects virtually did not make any prosaccade errors. Therefore, this variable was dropped from further analyses. Antisaccade error rate, pro- and antisaccade latencies as well as ICV of pro- and antisaccade latencies were normally distributed (all Kolmogorov–Smirnov tests $p>.11$). Table 3 displays means and standard deviations for all saccadic variables. In the repeated-measures ANCOVAs, there was neither a significant main effect of Order (nicotine first, placebo first) nor interactions of Order with any of the variables (all $p>.14$).

For prosaccade mean latency, there were no main or interaction effects (all $p>.18$). For ICV of prosaccade latency, there was a trend for a main effect of Treatment ($F(1,23)=3.78$, $p=.064$, $\eta_p^2=.14$) indicating lower prosaccade response time variability in the nicotine condition. No further main or interaction effects were observed for this variable (all $p>.15$).

For antisaccade error rate there was no main effect of Treatment ($F(1,23)=1.06$, $p=.31$). As expected the two groups differed in antisaccade error rates ($F(1,23)=34.93$, $p=5\times10^{-7}$, $\eta_p^2=.60$)

indicating the low accuracy probands performed worse than the high accuracy probands (Figure 1). There was an interaction effect of Treatment×Group ($F(1,23)=6.45$, $p=.018$, $\eta_p^2=.14$) indicating that low accuracy probands made fewer antisaccade errors in the nicotine condition than in the placebo condition whereas the high accuracy probands' performance did not differ between placebo and nicotine (Figure 1). Post hoc comparisons confirmed that nicotine decreased antisaccade errors in low accuracy probands ($F(1,12)=6.83$, $p=.023$, $\eta_p^2=.36$) but not in high accuracy probands ($F(1,12)=0.30$, $p=.596$, $\eta_p^2=.02$). There were no other main or interaction effects for this variable (all $p>.08$).

Figure 1 about here

For antisaccade latency there were no main or interaction effects (all $p>.09$). For ICV of antisaccade latency, there was no main effect of Treatment ($F(1,23)=0.04$, $p=.84$); however there was a trend for a Treatment×Eccentricity interaction ($F(1,23)=4.07$, $p=.056$, $\eta_p^2=.15$). Post-hoc comparisons showed a decrease in ICV of antisaccade latency under nicotine for the 12° eccentricity condition ($F(1,27)=4.52$, $p=.043$, $\eta_p^2=.14$) but not for the 6° eccentricity condition ($F(1,27)=0.03$, $p=.866$, $\eta_p^2=.001$). Moreover, there was a significant triple interaction of Treatment×Eccentricity×Group ($F(1,23)=5.39$, $p=.029$, $\eta_p^2=.19$), demonstrating that the interaction of Treatment×Eccentricity depended on the factor Group. Post hoc comparisons revealed that the interaction of Treatment×Eccentricity was significant in the low accuracy probands ($F(1,11)=4.97$, $p=.048$, $\eta_p^2=.31$) but not in the high accuracy probands ($F(1,11)=0.10$, $p=.755$, $\eta_p^2=.009$) (see also Figure 2). There were no further main or interaction effects (all $p>.23$).

Figure 2 about here, Table 3 about here

Discussion

The present study investigated the influence of nicotine on prosaccade and antisaccade eye movements in healthy, male, non-smoking volunteers stratified for low and high antisaccade performance. We did not detect a main effect of nicotine on antisaccade performance. However, nicotine enhanced antisaccade performance in low performing subjects, whereas it had no effect in high performing subjects.

Concerning antisaccade error rate, we found an interaction effect of nicotine and group status: nicotine reduced antisaccade error rate in the low performing group while leaving the performance of the high performing group unaffected. This finding is in agreement with the notion that baseline performance level may be a determinant of the cognitive effects of nicotine (Newhouse et al. 2004). However, we did not observe a detrimental effect of nicotine intake in the already high-performing subjects as proposed by the inverted U-shaped model by Newhouse et al. (2004). Possibly, our dose of nicotine was comparatively low; a larger dose of nicotine might have induced a performance decline in the high accuracy probands and might have led to an even greater performance improvement in the low accuracy group. It is also possible that our "high accuracy participants" exhibiting an average antisaccade error rate of about 15% in the placebo condition did not exhibit peak performance in this task and for that reason we did not observe a nicotine-induced performance decline in these participants. Psychometrically defined, an antisaccade error rate of 0% would represent optimal performance (i.e. 100% accuracy) and thus a floor effect leaving no further room for improvement by a substance such as nicotine. Therefore, it would be interesting to conduct a nicotine study in participants who might actually exhibit peak performance in the antisaccade task (i.e. who exhibit a very low error rate of less than 5%, ideally 0%). Possibly, in those participants a performance decline with nicotine administration will be more readily observable.

We also checked our data for a possible statistical phenomenon which might be a trivial explanation of the present data. In a repeated-measurement design in which subjects are tested twice, their scores tend to regress towards the mean. This regression to the mean (also known as the law of initial value) describes the statistical phenomenon that if a variable is extreme on its first measurement, it will tend to be closer to the average on a second measurement, and if it is extreme on a second measurement, it will tend to have been closer to the average on the first measurement (Bland and Altman 1994, Wilder 1958). This statistical phenomenon might also explain why initially low performing subjects improve on the second testing session and high performing subjects performing less well on the second testing session. We checked the present antisaccade error data for this issue by breaking down the three-way interaction of Treatment (placebo, nicotine)×Group (low accuracy probands, high accuracy probands)×Order (placebo/nicotine, nicotine/placebo). This interaction was not significant ($F(1,23)=3.36$, $p=.08$), though one could argue there is a trend towards significance. However, mean values revealed that probands with low accuracy always exhibited a lower antisaccade error rate in the nicotine condition regardless whether they received nicotine first or placebo first. Mean values from the probands from the group with high accuracy revealed that they showed a practice effect from Session 1 to Session 2: Those who received placebo at Session 1 showed poorer performance during the placebo session than during the nicotine session and those who received nicotine at Session 1 showed poorer performance during the nicotine session compared with the placebo session. These result patterns argue against a regression to the mean and in favor of the notions that the performance enhancement of the probands with lower accuracy can be attributed to the nicotinic treatment, whereas the pattern of mean values in the probands with high accuracy revealed that they displayed a practice effect which cannot be connected with the nicotine administration. In addition, the pattern of results regarding the response time variability of

antisaccade latency (i.e. ICV of antisaccade latency) also argues against a regression to the mean: The interaction Treatment × Eccentricity × Group × Order was also not significant ($F(1,23)=1.31$ $p=.27$).

We did not observe any nicotine effects on mean antisaccade latency, contrary to some previous studies (Ettinger et al. 2009; Larrison-Faucher et al. 2004; Rycroft et al. 2007). However, for intra-individual coefficient of variation (ICV) of antisaccade latency we did find a trend for an interaction of nicotine and eccentricity condition indicating a nicotine-induced decrease in variability of antisaccade latency for the 12° eccentricity condition only. There was also a significant three-way interaction of nicotine treatment, eccentricity condition and group for ICV of antisaccade latency. This three-way interaction indicated that the simple interaction of nicotine and 12° eccentricity condition was influenced by the factor group. Post hoc comparisons showed that the two-way interaction of nicotine and 12° eccentricity condition was only significant in the low performing group but not in the high performing group. There are two published studies examining the effects of stimulus eccentricity on antisaccade latencies in human subjects. In a study by Fischer and Weber (1997), a decrease in antisaccade latencies was seen with increasing stimulus eccentricity (ranging from 1° to 12° stimulus eccentricity). Fischer and Weber also found that antisaccade error rate increased with increasing eccentricity (Fischer & Weber 1997). On the contrary, Dafoe et al. (2007) did not find a significant effect of eccentricity on antisaccade latencies. However, Dafoe et al. (2007) found that a near stimulus eccentricity provoked more antisaccade errors than a far eccentricity condition. Given these contradictory findings on effects of eccentricity on antisaccade performance, we can only speculate why we found a specific effect of nicotine on a more distant 12° stimulus eccentricity condition. In the present study, there were no significant effects of eccentricity on antisaccade error rate and antisaccade latency, although mean values indicate that the 6° condition tended to

provoke more antisaccade errors and tended to lead to longer antisaccade latencies. Thus, we would have expected that nicotine effects will emerge on the (presumably) more difficult 6° condition. Therefore, the present finding of a decrease in variability of antisaccade latency for the 12° eccentricity condition only is somewhat unexpected. It is possible that the 12° condition is more sensitive to nicotine effects than the 6° condition. If one inspects the mean values of antisaccade error rate under placebo and nicotine in the low performing group, it becomes obvious that nicotine led to a reduction in antisaccade error rate of about 3% in the 6° condition, while there was a nicotine-induced reduction of antisaccade errors of about 10% in the 12° condition. Analogous to this tendency of a more pronounced effect of nicotine in the 12° condition for antisaccade errors, variability of antisaccade latencies was reduced with nicotine treatment to a greater extent in the 12° condition.

The effect of nicotine on response time variability also stresses the relevance of measuring parameters of intra-subject variability. Just as nicotine tended to decrease variability in prosaccade latency, the effect of nicotine on variability in antisaccade latency further underlines that measures of intra-subject variability might be useful in the investigation of disease-related endophenotypes and in the search for new pharmacological treatment targets. This notion is further supported by recent findings in a study testing the effects of methylphenidate in a stop-signal reaction time (SSRT) task in 24 healthy young men (Nandam et al., 2011). The SSRT is a task measuring response inhibition as this task requires subjects to cancel a prepotent "go" response upon presentation of an infrequent "stop" signal (Nandam et al., 2011). In that study, methylphenidate did not affect mean reaction time, rather methylphenidate decreased response time variability as measured by the ICV (Nandam et al., 2011). Similar to the effects of nicotine we found on ICV of antisaccade latency, the results by Nandam et al. (2011) argue against a

simple enhancement of motor or processing speed but indicate that the stimulant methylphenidate reduced behavioral variability in an executive task.

We did not find nicotine effects on mean prosaccade latency indicating that there was no general speeding in reaction time of saccadic eye movements by nicotine in our study. There was, however, a trend for a main effect of nicotine on intra-individual coefficient of variation (ICV) of prosaccade latencies revealing a tendency for a reduction in reaction time variability under nicotine. Possibly, this intra-subject reaction time variability or ICV might be a sensitive measure to detect nicotine effects in a similar way as measures of intra-subject variability were particularly impaired in patients with ADHD (Klein et al. 2006). The increased intra-subject variabilty in ADHD has been replicated consistently and is not part of a general performance decrement; rather, increased intra-subject variability seems to represent a specific deficit (Klein et al. 2006). Hence, parameters of intra-subject variability should be recognized in future drug-challenge studies beside the traditional measures of central tendency like the arithmetic mean.

The influence of baseline performance on subsequent response to a drug challenge has been previously discussed by a number of other authors (Kimberg et al. 1997; Mattay et al. 2000; Mehta, 2002; Mehta et al. 2000; Robbins and Sahakian, 1979) demonstrating that despite the absence of an overall effect of a drug, the drug might still be beneficial to a subgroup of individuals. Our results indicate that it might be useful to stratify probands in clinical trials according to their performance level in order to test the efficacy of a compound. Future clinical trials might stratify patients into subgroups with and without cognitive deficits or with more pronounced versus less pronounced deficits. Especially in disease states involving attentional and executive functioning impairments such as schizophrenia and ADHD, those patients exhibiting persistent and severe attentional deficits might benefit from adjunctive treatment with nAchR agonists. While acetylcholinesterase inhibitors have been found to ameliorate deficits in memory

and attention in schizophrenia patients (Ribeiz et al. 2010), the evidence on the partial α7 nAchR agonist DMXB-A is more ambiguous. DMXB-A improved some aspects of attention and memory in healthy subjects (Kitagawa et al. 2003) and in schizophrenia (Olincy et al. 2006), although it showed no effects on cognitive performance in another extensive study with schizophrenia patients (Freedman et al. 2008). Future studies might consider subdividing schizophrenia patients into a group of individuals with severe impairment and a group with only slight or no impairment. Results that further support this idea come from a study by Larrison-Faucher et al. (2004) which investigated the effects of nicotine on antisaccade performance in schizophrenia patients. Nicotine treatment significantly decreased antisaccade errors in task-impaired schizophrenia patients, whereas no nicotine effects were demonstrated for non-impaired schizophrenic subjects or controls (Larrison-Faucher et al. 2004). Although there is evidence for specific α7 nAchR pathophysiology in schizophrenia (De Luca et al. 2006; Freedman et al. 1995; Severance and Yolken, 2008), future clinical trials should also target at α3 nAchR as polymorphisms of the α3 subunits are associated with prepulse inhibition – another schizophrenia endophenotype and a measure of early attentional gating (Petrovsky et al. 2010).

Limitations of the present study include that double-blindness in our design was partially uncovered by the participants as they could correctly guess which patch they had received above chance level, especially after session two. Secondly, we appreciate the limitations of the median split approach. With turning a continuous variable into a categorical one there is reduced power to detect interaction effects due to loss of information in contrast to a regression approach. In addition, median splits are sample-dependent. Although the present study was adequately powered, future studies might want to opt for a regression model when analyzing what predicts a nicotine effect. Thirdly, we did not measure nicotine plasma levels, but we chose our nicotine dosages in line with previous studies. Fourthly, a larger dose of nicotine might have produced

larger performance changes in the subjects; therefore future studies might use higher nicotine doses preferably in combination with a nausea-preventing substance such as domperidone. Finally, it would also be of interest to conduct a multi-dose study in a stratified study population, similar to the study with repeated nicotine administration by Heishman et al. (2000): tolerance to the aversive effects of nicotine might develop with repeated exposure and performance changes might be more readily observed.

In conclusion, the present study showed that nicotine significantly enhanced antisaccade performance in the low accuracy probands while leaving performance of the high accuracy probands unaffected. The results are in favour of the notion that baseline cognitive performance influences the effect of acute nicotine administration in healthy non-smokers. Additionally, the findings suggest that stimulation of the nAchR system might be an effective way to treat deficits in executive control. Future studies on nicotine and nicotine-like drugs should account for inter-individual differences in task performance as this appears to be an important predictor of treatment effectiveness. Further research is needed to clarify other predictors of response to nicotinic stimulation such as genetic variation in nicotinic receptors.

Conflict of Interest

The work was neither supported by the tobacco industry nor by any pharmaceutical company. The authors declare that over the past three years KS has received compensations from AstraZeneca and Servier. The authors declare that over the past three years HW has received compensation from Jansen Cilag, Schattauer and the Netherlands Organisation of Scientific Research. All other authors declare no conflict of interest.

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Tables

Table 1 Timeline of the testing sessions

Before patch application:	Blood pressure measurement
	Visit study physician and informed consent (at session 1)
	Urine drug screening test
	Assessment of mood and physical symptoms with visual analogue scales
Patch application (7mg nicotine or placebo) and beginning of 3-hour-waiting time	
During waiting time:	Collect demographic data, verbal IQ testing and SCID-I interview
	Have a light lunch
	Allowed to read
After 3 hours:	Collect data on caffeine consumption
	Assessment of mood and physical symptoms with visual analogue scales
	Antisaccade testing
	Patch removal
	Let participant make a guess about patch identity
	Debriefing and financial compensation (at session 2)

Table 2 Sample characteristics by Group

	Low accuracy probands (*N*=14)	High accuracy probands (*N*=14)
Age (years)	30.50 (11.71)	25.71 (5.21)
Education (years)	16.21 (2.75)	16.29 (0.73)
Verbal IQ	126.07 (18.21)	111.57 (15.41)
BMI	24.04 (3.68)	23.97 (1.53)
Daily caffeine (mg)	31.07 (46.93)	39.00 (68.20)
Order of patch (*N* nicotine first / *N* placebo first)	5/ 9	8/6

Note. Data represent means (standard deviations) unless otherwise specified. The two groups did not differ in age, education, BMI, daily caffeine and order of patch (all p>.17), but they differed regarding verbal IQ (p=.03) indicating a lower verbal IQ in the high accuracy group.
Abbreviations: IQ, intelligence quotient; BMI, body mass index.

Table 3 Descriptive statistics of saccadic variables by Group, Treatment and Eccentricity

	Low accuracy probands (*N*=14)				High accuracy probands (*N*=14)				
	Placebo		Nicotine		Placebo		Nicotine		
	6° eccentricity	12° eccentricity	6° eccentricity	12° eccentricity	6° eccentricity	12° eccentricity	6° eccentricity	12° eccentricity	p
Prosaccade latency (ms)	168.51 (25.76)	182.77 (27.56)	171.35 (24.20)	187.79 (34.05)	173.27 (28.45)	190.84 (28.95)	170.39 (31.71)	189.75 (37.48)	n.s.
ICV of prosaccade latency	.20 (.07)	.21 (.06)	.21 (.07)	.22 (.07)	.22 (.07)	.25 (.10)	.21 (.09)	.22 (.11)	.064[a]
Antisaccade error rate (%)	49.30 (14.65)	36.36 (14.73)	45.88 (17.17)	26.00 (10.88)	19.87 (12.60)	8.93 (7.10)	21.70 (17.17)	11.02 (6.65)	.018[b]
Antisaccade latency (ms)	302.78 (33.64)	294.66 (43.25)	304.66 (30.37)	288.25 (31.36)	288.94 (44.34)	282.92 (49.27)	283.36 (44.81)	280.67 (45.19)	n.s.
ICV of antisaccade latency	.21 (.06)	.22 (.05)	.23 (.07)	.18 (.07)	.20 (.06)	.17 (.04)	.17 (.04)	.15 (.05)	.029[c]

Note: Table displays means (standard deviation) of all saccadic variables by Group (low accuracy probands, high accuracy probands), Treatment (placebo, nicotine), and Eccentricity (6° eccentricity, 12° eccentricity). n.s.=not significant.

[a] Trend for a main effect of Treatment: placebo > nicotine

[b] Treatment×Group interaction: nicotine decreased antisaccade error rate in the low accuracy group (p=.023), but not in the high accuracy group (p=.596)

[c] Treatment×Eccentricity×Group interaction: nicotine decreased ICV of antisaccade latency in the 12° eccentricity condition (p=.043), but not in the 6° eccentricity condition (p=.866). Above interaction of Treatment×Eccentricity was significant in the low accuracy probands (p=.048), but not in the high accuracy probands (p=.755).

Figures

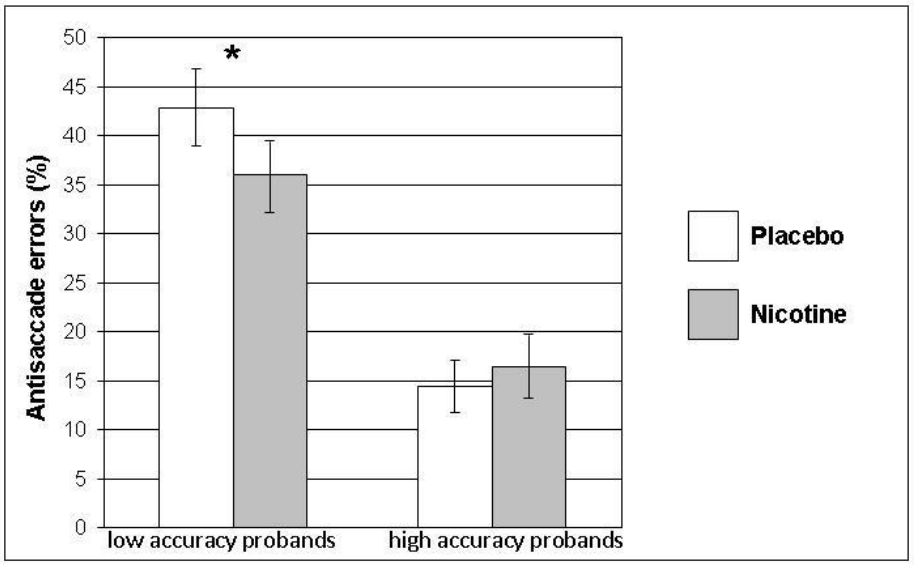

Figure 1. Percentage antisaccade errors in the low and high accuracy subgroups during placebo and nicotine treatment. Error bars refer to ±SE. Nicotine significantly reduced antisaccade error rate in the low accuracy probands (p=.023), but not in the high accuracy probands (p=.596).

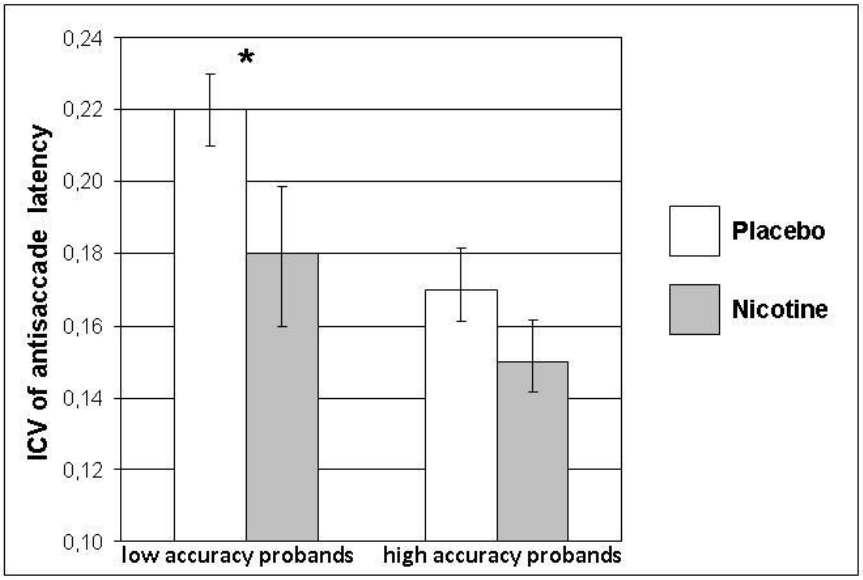

Figure 2. Intra-individual coefficient of variation (ICV) of antisaccade latency for the 12° eccentricity condition in the low and high accuracy sub-groups during placebo and nicotine treatment. Error bars refer to ±SE. Nicotine significantly decreased ICV of antisaccade latency in the low accuracy probands (p=.048), but not in the high accuracy probands (p=.755).